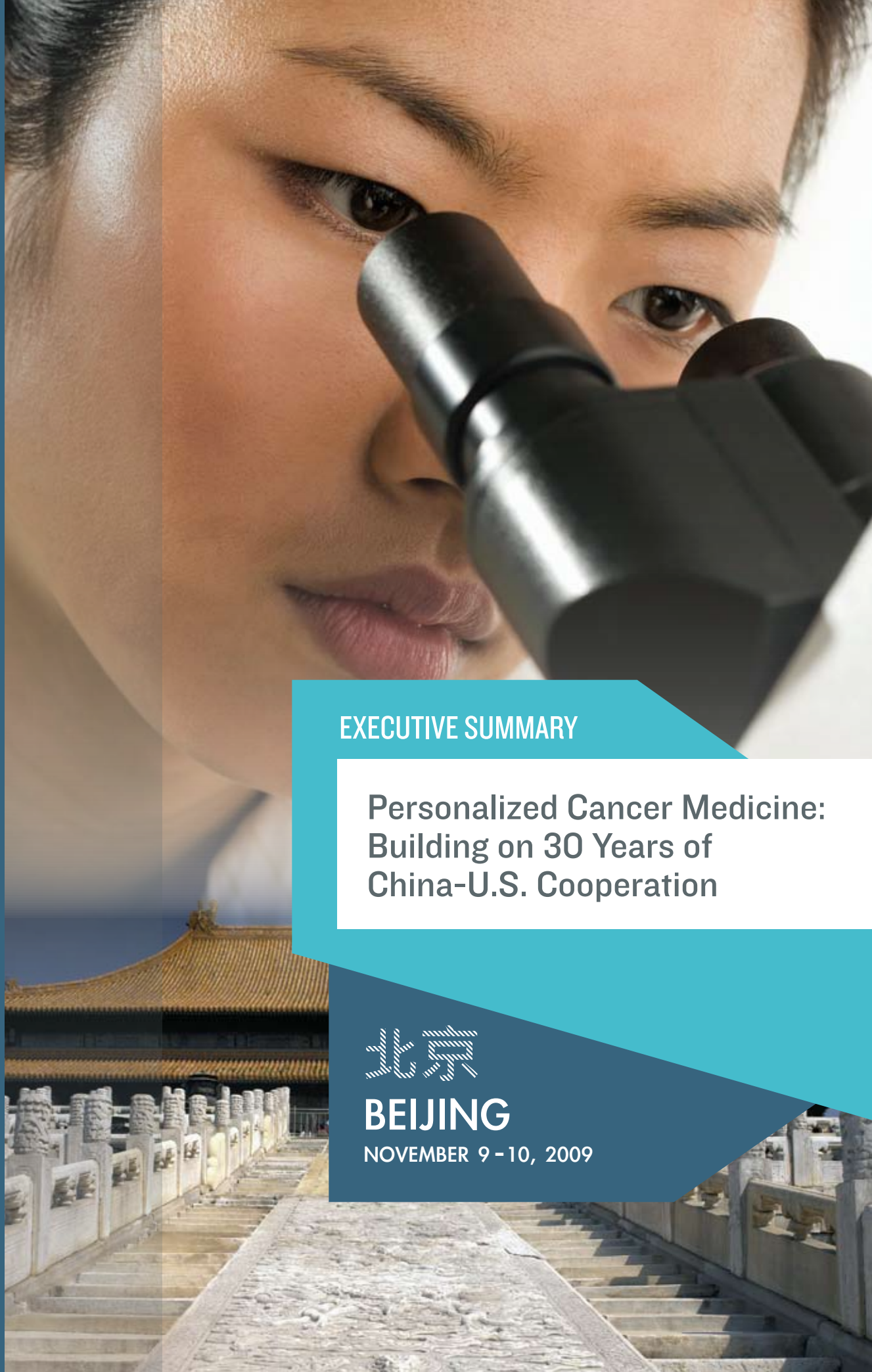
National Cancer Institute



EXECUTIVE SUMMARY

Personalized Cancer Medicine: Building on 30 Years of China-U.S. Cooperation

北京

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

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执行摘要

History

This symposium commemorated the 1979 meeting of the former Director of the U.S. National Cancer Institute (NCI) and the Director of the Cancer Institute/ Hospital of the Chinese Academy of Medical Sciences (CICAMS) several months after President Jimmy Carter and China's leader Deng Xiaoping signed the United States–China Agreement on Science and Technology. The discussion between the NCI and CICAMS directors launched the start of government-to-government research and exchange programs and established a framework for cancer research collaboration between the United States and China.

Purpose

The purpose of the symposium was to highlight the accomplishments of several past and ongoing United States–China cancer research studies, and bring together thought leaders from both countries who are working in several scientific and technology areas driving the development of personalized cancer medicine. Participants at the meeting identified several grand challenges and opportunities for the United States and China to work together to enable a future of personalized cancer medicine.

Urban areas such as Shanghai are experiencing rapid increases in cancers that are most common in Western countries such as breast and colon cancer.

Background

Presenters summarized the burden of cancer to both countries, and how U.S.–China cooperation provides unique opportunities to advance research that will ultimately benefit cancer patients around the world. Speaking by video message, U.S. Department of Health and Human Services (HHS) Assistant Secretary for Health Dr. Howard Koh emphasized that cancer is a major public health issue in the developing world, because more than 50% of new cancer cases and nearly two-thirds of cancer deaths occur in developing countries. Chinese Minister of Health (MOH) Dr. Zhu Chen highlighted his nation's recent efforts in health care reform, and noted that the complexity and threat of cancer requires a global perspective and participation. He further noted that enhancing collaboration in many areas of biomedical research will deepen the relationship between the United States and China and foster the development of new generations of scientists.

More than 50% of new cancer cases and nearly two-thirds of cancer deaths occur in developing countries.

Chinese speakers—including Professor Qian Liu, Vice Minister, and Professor Wei He, Director General, MOH Department of Science and Education, and Ping Zhao, Director of CICAMS –reviewed the cancer problem in China. Professor Liu noted that there are more than 2.2 million deaths from cancer in China each year. Director Zhao referred to the situation in China as a cancer epidemic, now that cancer is the leading cause of death in urban and rural areas. NCI Deputy Director Anna Barker noted that although lung cancer has the highest mortality rate in both the United States and China; in China, liver, stomach, and esophagus are the next most deadly cancer types as contrasted with colon, breast, and prostate cancer in the United States. Several Chinese speakers explained that a series of factors in China will likely contribute to increases in cancer rates such as an aging population, dietary changes, environmental hazards, hepatitis B, and smoking.

Several Chinese experts emphasized the importance of cancer prevention and control. MOH published a plan of cancer prevention and control in 2004 that included enhancing the country's cancer registration system, as well as providing health education, screening, and early diagnosis and treatment for patients. MOH is currently devising a new plan of action which will span from 2010 to 2020

and will further enhance the country's cancer registration system.

U.S. National Institutes of Health (NIH) Director Dr. Francis Collins, speaking by video message, noted China's contributions to the Human Genome Project and the International Haplotype Map Project, and affirmed that China is poised to be an important player in the development of personalized cancer medicine. Drs. Depei Liu, President of the Chinese Academy of Medical Sciences (CAMS), and Qimin Zhan, Vice President of CAMS, strongly supported building cooperation in the area of personalized cancer medicine. President Liu cautioned that many cancers in China occur in low-income populations and expressed the hope that advances in personalized medicine will inform the development of adaptive technologies that are affordable for middle- and lower-income families.

There are more than 2.2 million deaths from cancer in China each year.

Achievements to Date

In the first part of the meeting, speakers highlighted achievements from past and existing studies in China that NCI has supported and/or participated in, particularly in the area of cancer epidemiology.

Existing NCI-Supported Studies in China: Building on Unique Research Opportunities

Several speakers discussed the advantages to conducting cancer research in China. Professor Yu-Tang Gao, Shanghai Cancer Institute and Dr. Wei Zheng, Vanderbilt University, summarized unique opportunities for epidemiology research in China including: unique cancer patterns, high participation rate of study subjects, low attrition rates, and different population characteristics relative to Western cohorts. For example, Chinese populations exhibit several key lifestyle differences relative to American populations that may affect cancer risk, such as diet and exercise.

Relatively low levels of admixture among Han Chinese—and the opportunity to replicate scientific findings generated in American populations—are particularly valuable for genetic studies, including genome wide association studies (GWAS). As described by

NCI's Dr. Ann Hsing, cancers such as biliary tract cancers are more common in Asian populations and are increasing rapidly in Shanghai. In addition, urban areas such as Shanghai are experiencing rapid increases in cancers that are most common in Western countries such as breast and colon cancer.

NCI's Dr. Curtis Harris reported that the high rates of hepatocellular carcinoma in Qidong, Jiangsu Province provided an opportunity to discover an unusually high frequency of G-to-T (AGG->AGT) nucleotide transversions in codon 249 serine of the p53 gene. Further analysis revealed that that exposure to dietary aflatoxin B1 was the likely cause of these mutations during liver carcinogenesis.

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Epidemiological Investigations

NCI's Dr. Philip Taylor reported how earlier NCI-supported studies in China targeted geographical areas with high incidences of certain cancers based on data from the 1976 *Atlas of Cancer Mortality in China*. Results from the Nutrition Intervention Trial in Linxian, Henan Province, showed that the supplement containing selenium, vitamin E, and beta-carotene decreased total mortality, cancer mortality, and gastric cancer mortality. Beneficial effects of a supplement were evident up to 10 years after cessation of supplementation. Studies of gastric cancer in Linqu, Shandong Province, reviewed by Professor Wei-cheng You, Peking University, found that treatment of *H. pylori* infections reduced the prevalence of precancerous gastric lesions. Other studies, such as those addressing cervical cancer in Shanxi Province described by Professor Youlin Qiao, CICAMS, focus on introducing cost-effective screening technologies in China. All three of these studies identified cancer prevention strategies of public health significance.

Other NCI-supported studies in China have investigated populations that have experienced unique environmental or occupational exposures. Professor Youlin Qiao described screening studies of tin miners in Yunnan Province with unusually high rates of lung cancer, and NCI's Dr. Qing Lan described studies of the effect of benzene exposure on factory workers in different parts of China. The benzene studies informed the development of new regulations to lower benzene occupational exposure in China and influenced the risk

assessment process and regulatory action in the United States such as rules reducing the benzene content of gasoline.

Genetic Studies

Several of the epidemiological studies described above have completed genetic analyses in recent years. Dr. Wei Zheng described how a GWAS study using data from the Shanghai studies identified a single nucleotide polymorphism (SNP) located upstream of the *ESR1* gene on chromosome 6q25.1 that showed a strong and consistent association with breast cancer. Dr. Ann Hsing described an association study using a candidate gene approach that identified 14 SNPs in the inflammation pathway, including COX-2, IL8, and TNF, that were associated with increased risk of biliary tract cancer and stones. NCI's Dr. Qing Lan described studies indicating that individuals with certain polymorphisms in genes that activate and detoxify benzene metabolites had decreased white blood cell counts at relatively low levels of benzene exposure. Professor Wei-cheng You reviewed research that identified polymorphisms in genes involved in cytokine production, DNA repair genes, and the COX-2 promoter region, that increase the risk of gastric cancer in combination with certain environmental factors.

Training

In addition to highlighting the achievements of specific research studies, speakers—including Dr. Roger Glass, NIH Fogarty International Center and Dr. Robert Wiltrout, NCI—recognized the role of the NCI intramural program in training hundreds of Chinese-born researchers. Many of these individuals have returned to China in recent years to assume scientific leadership positions in China and maintain active individual collaborations with American researchers.

State-of-the-Science and Challenges for Developing Personalized Cancer Medicine

During the second part of the meeting, American and Chinese speakers reviewed the state-of-the-science for several technologies driving personalized cancer medicine. Several important themes emerged from this discussion that offer opportunities for new scientific partnerships.

The Many Applications of Personalized Cancer Medicine

Several speakers discussed how advanced technologies can be used to develop different applications for personalized cancer medicine. Dr. Ronald DePinho, Harvard Medical School, highlighted the potential for developing new methods for early detection and identifying tumor subsets, and administering appropriate therapy regimens to patients. Using the example of prostate cancer, he emphasized the value of using genetic information to identify tumors most likely to metastasize. Of the 220,000 cases of prostate cancer identified each year in the United States, only 27,000 of these cases progress to a lethal, metastatic form. Dr. DePinho argued that if tumors likely to progress can be identified using molecular markers, patients with these tumors could be treated aggressively as early as possible, and patients with tumors unlikely to metastasize could be spared overtreatment. He further stated that this approach should be feasible as genetic determinants of cancer progression are acquired early in tumor development.

NCI's Dr. Gary Kelloff applied similar reasoning to developing new cancer prevention agents. Detailed study of pre-cancerous lesions such as intraepithelial neoplasia (IEN) at the genetic level can be used to identify high-risk cohorts who would be suitable candidates to receive cancer preventative agents.

Dr. Joshua LaBaer, Arizona State University, highlighted the value of developing protein-based diagnostics based on detailed functional knowledge to sort patients into different disease subtypes. These diagnostic technologies should be capable of monitoring the ongoing clinical state of patients so that changes to molecular signatures can be tracked throughout the course of disease.

Several speakers—including Dr. Paul Mischel, UCLA, and Dr. David Parkinson, Nodality—emphasized the value of using advanced technologies to understand tumor heterogeneity within a single patient. This heterogeneity occurs at multiple levels: the tumor cell, the microenvironment, and the host. Both Drs. Mischel and Parkinson described new techniques to isolate and characterize different subsets of tumor cells within a single patient, information that can be used to improve the understanding of cancer pathways, and potentially inform the development of combination therapy regimens tailored to individual patients. They also emphasized that tumor heterogeneity is critical to the evolution of therapeutic resistance, as

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tumors experience strong selective pressure to enhance growth of tumor cell subsets that are not killed by a particular drug.

From DNA Sequence Data to Biological Understanding

Several speakers—including Dr. Joe Gray, Lawrence Berkeley National Laboratory, Professor Huanming Yang, Beijing Genomics Institute-Shenzhen, Professor Guoping Zhao, Chinese National Genome Center at Shanghai, and Dr. Jim Heath, Caltech, Dr. Jonathan Weinstein, MD Anderson—noted that new sequencing technologies would likely reduce the cost of sequencing a single genome to a few thousand dollars within the next several years. These cost reductions are fundamentally changing the types of scientific questions that can be asked and are leading to the production of vast amounts of genetic data.

Cost reductions in DNA sequencing are making the expansion of projects such as The Cancer Genome Atlas (TCGA) project economically and logistically feasible. TCGA is generating large amounts of genomic data to develop a "parts list" for many types of tumors. However, these data must be converted into biologically meaningful information. Speakers such as NCI Director Dr. John Niederhuber, along with Drs. Barker, Chin, Gray, and Weinstein, explained that a new generation of scientists is needed to develop novel computational analysis tools for multidimensional data analysis. In addition, Drs. DePinho, Gray, and Chin emphasized the need to develop high throughput strategies for collecting functional genomic information using cell lines and animal models to understand cancer pathways and networks. Dr. Paul Mischel, UCLA, suggested that innovative technologies such as using the

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DNA-encoded antibody library (DEAL) arrays can be used to obtain functional information directly from clinical samples, although NCI's Dr. Carolyn Compton explained several challenges involved in the collection and management of clinical biospecimens for studies in molecular medicine.

Integrating Somatic and Germline Genomic Information

Several speakers including Drs. Gray, Heath, DePinho, and Mischel emphasized the importance of understanding genetic variations at the level of the tumor cell, the microenvironment, and the host to develop personalized interventions. Both somatic tumor sequencing studies and investigations of germline genetic variation are needed to understand the impact of the full spectrum of genetic contributions to cancer. Several speakers—including Dr. Dongxin Lin, CICAMS, along with Drs. Zheng, Hsing, Yang, and Guoping Zhao—described studies addressing the role of germline variation on cancer risk and/or response to therapy.

During the panel discussion at the end of the meeting, Dr. Chin suggested that the United States and China should develop new partnerships to design integrative analyses of somatic and germ-line genetic variation. These analyses may be particularly fruitful in studies of cancers such as lung cancer, where there is evidence that genetic differences among geographical populations may influence response to therapy.

Opportunities and Challenges for Protein Biomarker Analysis

Several presentations described strategies to identify and measure protein biomarkers for cancer. Professor Yanning Gao, CICAMS, described a method to identify serological markers for lung cancer from blood, but noted the difficulty of isolating these biomarkers because they constitute an extremely small proportion of all circulating proteins in blood. Dr. LaBaer described his laboratory's approach to identify biomarkers based on detailed functional understanding of proteins using technologies such as protein arrays developed based on knowledge of the human genome sequence.

Dr. Heath explained that individual protein biomarkers are unlikely to predict cancer progression or outcome accurately. However, current methods for quantitative measurement of protein biomarkers are still quite expensive. Dr. Heath emphasized the need to develop new technologies using microfluidics to allow accurate and cost-effective methods for measuring panels of protein biomarkers on large numbers of clinical samples.

Pathways to New United States–China Cooperation

Meeting participants identified several opportunities to develop pilot projects to enhance United States–China cooperation in the area of personalized cancer medicine, including:

China–United States Working Group for Personalized Cancer Medicine

Participants recommended organizing an active working group of U.S. and Chinese scientists who could meet regularly and continue to discuss opportunities for increasing cooperation in the area of personalized cancer medicine. This group could plan follow-up workshops of American and Chinese scientists and inform the design and implementation of partnerships in this area.

Computational Analysis

Several participants noted that there are insufficient numbers of scientists worldwide who can conduct multidimensional analysis of genomic and epigenetic data. Building on the strength of China's educational system for developing talent in mathematics and computation, the United States and China should build a program to support scholar exchanges and collaborative research in this area.

Cancer Genomics

Meeting participants suggested that United States and China should work together to explore the development of a bilateral program in cancer genomics. This program would integrate somatic and germline information and support comparative analysis between U.S. and Chinese populations. This pilot model should explore how to share and exchange samples and data and develop workshops, training and/or exchange programs to improve understanding and communication between American and Chinese cancer genome experts, and form the basis for an ongoing exchange of ideas in this area.

Biobanking

Several Chinese scientists expressed a strong interest to collaborate with the NCI in developing and implementing biobanking standards on an international level. Biobanking is of increasing interest in China and there have been discussions about initiating large-scale efforts in this area.

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